

Pharmacoeconomics of Cancer Therapies: Considerations With the Introduction of Biosimilars

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Biologics are important treatments for a number of cancers, but they are also significant drivers of globally escalating healthcare costs. Biosimilars have the potential to offer cost-savings with comparable efficacy and safety to innovator products. They are being used in the European Union, Canada, Japan, and Australia and may help with improving health outcomes while minimizing costs to patients and global healthcare systems. The overall value of a biosimilar is not determined solely by its pricing. Efficacy and safety relative to the reference biologic drug and competitive agents as well as development and manufacturing costs, treatment administration costs, and results from long-term safety monitoring are considered. Optimizing economic efficiency is one part of an ongoing healthcare decision-making process with all therapeutics that aims to attain high levels of quality-of-care and safety given available resources. Some analytic tools stakeholders use to determine the pharmacoeconomic value of a therapy that are highlighted in this review article are opportunity cost, cost-effectiveness, and cost-minimization analyses. These methodologies can provide information to physicians, patients, and payers that may help reaffirm the value of a given biosimilar compared with its reference product throughout its life cycle.

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The prevalence of cancer is expected to increase worldwide over the next decade.¹ The incidence of new cases is expected to escalate from 11.3 million in 2007 to 15.3 million in 2030.¹ This increase may be 10-fold higher among the elderly (persons aged ≥65 years) than among younger individuals.² The treatment of cancer is already the foremost driver of increased healthcare costs in many countries.³ In the United States, increasing unit treatment costs per patient dominate as the driver for overall healthcare costs,³ despite

a decrease in overall cancer prevalence from 1999 to 2010.⁴ The US budget for cancer drugs as determined by sales rose fourfold from 1998 to 2008; most of these drugs are high-cost biologic drugs.⁵ For example, US Medicare spending on drugs administered in a physician's office, most of which were cancer treatments, rose 267% from 1997 to 2004, while overall Medicare spending rose only 47%.³ Many patients also may have faced escalating healthcare costs in excess of inflation, including insurance premiums (131% increase since 1999) and the potential for bankruptcy in some cases (Figure 1).³ It has been estimated that the percentage of the US family budget spent on healthcare in 2010 is identical to that spent on food.⁶ This places a significant burden on patients and their families.

The economic burden of cancer treatment is not limited to the United States. In France, the cost of cancer therapies has been doubling every 4 years, rising from €474 million to €975 million from 2004 to 2008.³ A significant driver of these increased healthcare expenditures may be treatment costs for aging patients with cancer^{3,7} or the longevity of this population increasing with economic expansion.⁷ This article will highlight specific economic considerations with biosimilars. Specifically, it provides insight into factors affecting the potential impact of biosimilars on healthcare costs. Considerations that are highlighted

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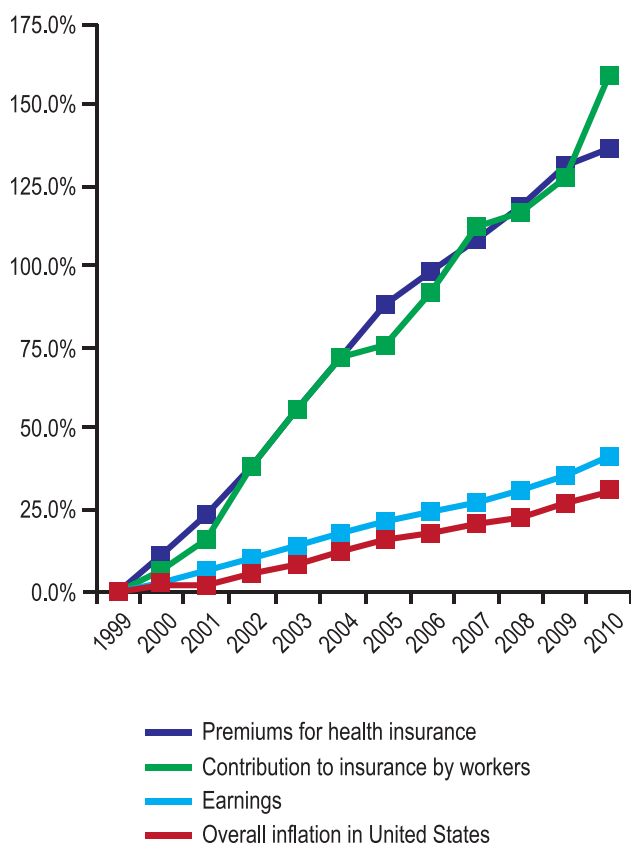


Figure 1. Escalating costs of insurance premiums and employee healthcare contributions compared with employee earnings and inflation, 1999 to 2010. Cornes P.³ With kind permission from Springer Science+Business Media: *Targeted Oncology*, The economic pressures for biosimilar drug use in cancer medicine, 7, 2012, S59, Cornes P, Figure 1.

include pricing and reimbursement, as well as available types of pharmacoeconomic methodologies that may be applicable to biosimilars (eg, cost-minimization and cost-effectiveness analyses).

HOW HAS THE BURDEN OF ESCALATING TREATMENT COSTS BEEN ADDRESSED SO FAR?

Because of escalating healthcare costs, many countries have enacted legislation authorizing the manufacture and distribution of small-molecule generic drugs. In many countries, including the United Kingdom, Germany, Sweden, France, and the Philippines, small-molecule generic drugs substantially reduced costs compared with their reference small-molecule drug. In many cases, the cost-savings were upwards of 50%.⁸ In the United States, the use of generics has increased since the initial enactment of the Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Amendments) in 1984. It is estimated that drug costs were reduced by \$1.32 billion annually for

each 1% increase in generic prescribing, and generics saved Medicare part D and its beneficiaries \$33 billion in 2007.^{3,9}

By 2016 approximately \$64 to \$67 billion worth of total global sales of biologic therapies will be coming off patent in the United States and the European Union (EU); a number of these are used to treat cancer.^{10,11} According to one estimate, an annual savings of €1.6 billion per year has been predicted for the EU if biosimilars to five patent-expired biologic drugs are successfully developed.³ Because of the high treatment costs associated with biologic drugs,⁵ several governments including those of the United States, EU, Japan, and Korea have instituted approval pathways for the development and commercialization of biosimilars.^{9,12} Biosimilars are not “generic” versions of currently approved biologics. A biosimilar is a biologic drug that is highly similar (ie, the two drugs have the same drug target, mechanism of action, and primary structure among other molecular similarities) to an approved reference biologic drug (originally patented drug or innovator product).¹³

Biosimilars have the potential to lower costs. However, due to their higher manufacturing and development costs, decreases are likely to be smaller in magnitude compared with generics.^{9,14} Biosimilars may increase patient access to potentially valuable therapies.⁹ In Germany, approximately one-third of prescriptions for the granulocyte colony-stimulating factor (G-CSF), filgrastim, were for its biosimilar in 2009.¹⁵ Using the biosimilar over the reference biologic drug resulted in significant savings; €1203.5 for the original filgrastim versus €867.8 for its biosimilar ($P < .0001$) according to one estimate.¹⁶ In the United States, projected savings from biosimilars range from \$3.0 to \$4.5 billion annually, and up to \$378 billion over the next two decades.³

The uptake of biosimilars in US oncology practices (and other areas where they are emerging) ultimately may depend on several considerations, including pharmacovigilance and safety profiles,^{9,17} the education of healthcare professionals and patients,⁹ and affordable pricing.⁹ The potentially lower cost of biosimilars may improve patient access to care and contribute to a shift in treatment strategies. In the United Kingdom, Germany, and the Netherlands, the availability of a lower cost biosimilar to G-CSF correlated with 10% to 20% increased use of a G-CSF agent. Along with the increase, G-CSF was used *earlier* in the course of therapy, resulting in a shift of its use as a secondary to primary prophylactic agent against febrile neutropenia.¹⁸ This is an example of how the affordability of biosimilars has the potential to provide patients with greater access to biologic drugs.

WHAT PHARMACOECONOMIC CONSIDERATIONS MAY AFFECT THE USE AND INCORPORATION OF BIOSIMILARS INTO CLINICAL PRACTICE?

As biosimilars emerge in the United States and EU after patents expire for several biologics,¹⁰ they may offer different opportunity costs to patients and healthcare systems in the treatment of cancer.³ An opportunity cost is a benefit foregone when a given option is selected over its next best alternative. In healthcare, opportunity cost analyses consider the level of resources currently devoted to a therapy that would otherwise be used in another manner.¹⁹ These analyses typically are performed by payers. Because of their comparability to their respective reference biologic drugs, biosimilars may increase patient access to treatment, while reducing opportunity costs for additional therapeutic options or other expenses.^{9,19}

Pharmacoeconomic considerations within healthcare systems may factor into the use of biosimilars for many countries.²⁰ An increasing number of countries have developed guidelines that specify standards for conducting economic evaluations to be included in reimbursement applications.²¹ The pharmacoeconomic studies that are the most pertinent to biosimilars will depend on the properties of the biosimilar and reference biologic. In this review, four types of pharmacoeconomic analyses are considered²⁰ that may be applicable with respect to biosimilars; cost-effectiveness, cost-minimization, cost-utility, and cost-benefit (Table). Appropriately designed and powered clinical studies demonstrating highly similar efficacy and safety profiles between a biosimilar and the reference biologic allow a cost-minimization analysis that would help determine the least expensive therapy (Figure 2).

Few articles are available in the literature regarding pharmacoeconomic analyses of biosimilars, especially biosimilars of monoclonal antibodies. A limited number of cost-minimization analyses have been

documented for biosimilars in certain countries where they are in use, such as the United Kingdom.²⁰ But, in the United States, cost information is not available because biosimilars are not yet approved. Of note, the US Food and Drug Administration (FDA) recently approved Teva's tbo-filgrastim, a short-acting G-CSF product. Tbo-filgrastim is marketed in Europe under the trade name Tenvagra-stim as a biosimilar G-CSF. Since a US biosimilar pathway was not in place at the time of FDA submission, Teva will market tbo-filgrastim as an innovator product in the United States.²² Payers may utilize cost-minimization analyses that also can be used to help other healthcare professionals identify treatment strategies that are beneficial to patients in terms of therapeutic value and cost. For example, a recent study compared the benefits of the use of low-cost versus high-cost bypassing agents that have demonstrated similar efficacy profiles in hemophilia surgical patients susceptible to inhibitors. (Bypassing agents are coagulation factor products that may avoid the insufficient activation of factor X in typical hemophilia.²³) The model used by the study authors examined drug cost and dosing over 14-day surgical procedures. The use of the lower-cost bypassing agent resulted in a decrease in total drug cost of 58% and a cost-savings of more than \$470,000.²⁴ As biosimilars emerge and are accepted by clinicians, cost-minimization models may provide insight into the value of biosimilars in terms of cost and clinical benefit.

FACTORS THAT MAY IMPACT PHARMACOECONOMIC ANALYSES OF BIOSIMILARS

The value of a biosimilar to society must be viewed from the perspective of healthcare providers, patients, and payers, and may be affected by several variables. Concentration on costs is not sufficient in itself, instead it is factored into an analysis that is

Table. Definitions of Selected Frequently Used Pharmacoeconomic Analyses

Type of Analysis	Definition
Cost-effectiveness	Comparison that balances a single unit of cost against a single unit of risks or benefits to the quality of life extended to the patient ²⁰
Cost-minimization	Comparison of multiple drugs of equal efficacy and equal tolerability to identify the least expensive therapy ²⁰
Cost-utility	Ratio between the cost of a health-related intervention and the benefit it produces in terms of number of years lived in full health ²⁰
Cost-benefit	Determines whether an investment or policy decision is sound (justification/feasibility) and provides a basis for evaluating policies by comparing the total expected cost of each option against the total expected benefits, to see whether the benefits outweigh the costs, and by how much; vaccination programs are a classic example ³³

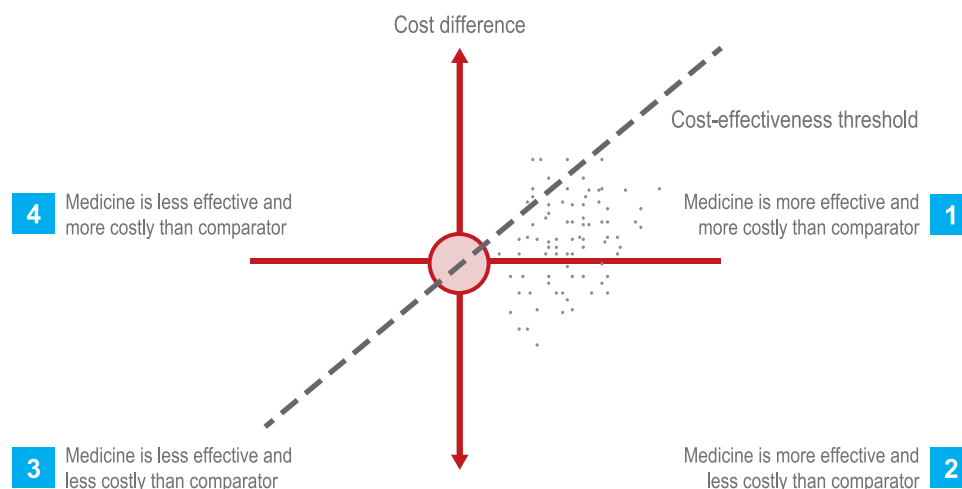


Figure 2. Cost-effectiveness plane. Ideally, most medications would fall in the upper right quadrant or in cases where efficacy is comparable and the medicine is less costly (eg biosimilars vs reference biologic drug), the points would be in the second quadrant. Simoens.²⁰ Reproduced with permission of Dove Medical Press in *Clinicoecon Outcomes Res*, 2011;3:29-36, via Copyright Clearance Center.

designed to assess the contribution of a therapy to improved patient well-being and health (Figure 3).³

Emergence of Second-Generation Biologics

The emergence of second-generation biologics (or biologics that make improvements on existing biologics through pegylation, alternative formulations, or other means)¹⁴ may affect the value of not only first-generation reference biologics, but also their biosimilars. As research and development of biologics in the oncology setting continues, newer, second-generation biologic drugs may offer different clinical properties compared with currently approved reference biologics. They may include new formulations, different efficacy profiles and/or dosing regimens, or reduced immunogenicity.¹¹ A second-generation biologic may have an improved efficacy and/or safety profile, but if the efficacy and safety of a given second-generation drug is comparable to the first-generation drug or its biosimilar, a cost-minimization analysis could be performed to identify the most economical solution for patients and payers. In contrast, cost-effectiveness comparison analyses could be performed with novel biologics that have different efficacy and/or safety profiles relative to first-generation products or their biosimilars. The results of pharmacoeconomic analyses that incorporate second-generation biologic drugs may affect the value that biosimilars of first-generation reference biologic drugs offer patients with cancer and healthcare providers. This may include the extent of financial and opportunity costs offset by the emergence of these therapies. For example, if a second-generation biologic has improved efficacy, the opportunity for the patient to have a better outcome would possibly negate its higher cost. In

addition, the emergence of second-generation biologic drugs may affect the drug acquisition prices for first-generation reference biologic drugs and their biosimilars.

Drug Acquisition Prices

Relative costs of biologic drugs also are reflective of drug acquisition prices (eg, manufacturers' wholesale list prices and additional costs less any discounts).²⁵ Differences in acquisition prices between a biosimilar and its reference biologic drug may vary, for example, due to differing research and development costs for a given biosimilar compared with another with the same reference biologic drug.²⁰ Any differences potentially could affect cost-minimization analysis results. Further, a price differential for a biosimilar could be substantial when compared

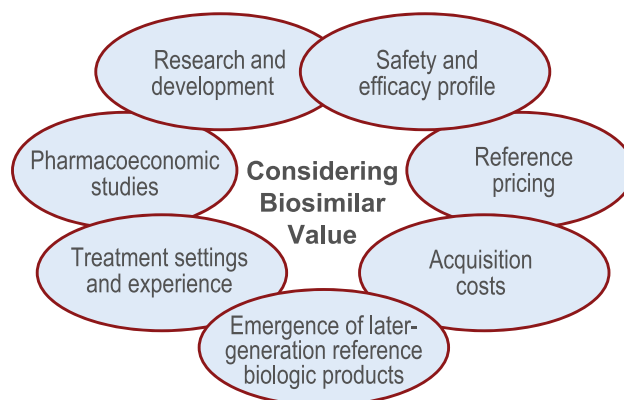


Figure 3. Factors that may be considered as part of the evaluation of the value of a biosimilar by healthcare community members. Cornes³; Zelentz et al⁹; Dranitsaris et al¹¹; Weise et al¹⁴; Simoens²⁰; NYS Department of Health²⁵; Kliff²⁶; Hoadley²⁹; Ebberts et al.³⁴

with a reference biologic and may increase as biosimilar pricing has the potential to fall with rising market share.²⁰ Hospitals may negotiate discounted biosimilar pricing (or that of other drugs) with manufacturers, creating competition in the distribution chain rather than direct price competition.²⁰ These variables can factor into pharmacoeconomic analyses within a given institution or when making comparisons between institutions. Due to these economic pressures, independent community oncology practices—which may be more cost- and time-efficient—are increasingly migrating toward the hospital-based/owned structure.

Treatment Administration Settings

The cost and subsequent value of a biosimilar may be affected not only by institutional discounting, but also by the type of institutional setting. The administration of biologics and/or their biosimilars through outpatient oncology clinics, which are traditionally less costly settings than hospitals, potentially can impact the value of a biosimilar and the results of pharmacoeconomic analyses. For example, outpatient oncology clinics may represent a lower-cost treatment option to patients and payers for the administration of expensive chemotherapeutics. However, this dynamic is evolving, as reimbursement to these centers is subject to changes in federal funding levels, as seen in the recent sequestration budget cuts in the United States to Medicare. Ultimately, these patients may shift to the hospital setting, where treatment administration costs are higher.²⁶ This would result in a potentially reduced cost-minimization benefit to the payer and/or patient for the reference biologic drug or its biosimilar.

Benefits Via Reduced Opportunity Costs

Reduced costs in terms of development or services associated with biosimilar use may lead to reduced opportunity costs when healthcare providers prescribe and administer biosimilars as opposed to reference biologics. From a patient perspective, the potential economic benefit of biosimilars may be determined on the basis of reduced treatment costs with highly similar efficacy to a reference biologic, thereby reducing opportunity costs for other expenses. All of the above considerations may provide patients, healthcare providers, and payers with the data and means for slowing increases in cancer treatment costs, while maintaining a focus on patients.

EVALUATING THE POTENTIAL ECONOMIC BENEFITS OF BIOLOGICS AND BIOSIMILARS

Economic evaluations are one part of a body of clinical evidence that can help inform the development

and use of safe and cost-effective biologics and biosimilars, while helping to optimize expenditure.²⁰ They may help healthcare community members synthesize information about the effectiveness, potential limitations, and costs of interventions as well as the value of their benefits.²⁷ In the United States, pharmacoeconomic studies on public health policies have been limited in scope to date; that said, certain advisory bodies, like the Advisory Committee on Immunization Practices, do explicitly consider economic evaluations when making recommendations.²⁷

Comparative Effectiveness Studies

Comparative effectiveness studies, where researchers examine the available evidence about the benefit and potential safety considerations of each therapeutic choice for different groups of individuals from existing clinical trials, clinical studies, and other research²⁸ have been used by several nations, including Australia, Canada, Germany, and the United Kingdom.²⁹ Each nation using these studies has an agency charged with undertaking comparative effectiveness studies and making recommendations to government health programs.²⁹ A prominent example of such an agency is the United Kingdom's National Institute for Health and Clinical Excellence (NICE).²⁹ A panel of experts drawn from academia, public health, practicing physicians, and other stakeholders, including consumer representatives, evaluate newly approved drugs through systematic reviews of available research and decide whether or not the given biologic or its biosimilar is recommended for reimbursement by the National Health System (NHS).²⁹ Drugs that are not recommended for reimbursement remain available to patients, but are not covered by the NHS.²⁹ Recommendations to the NHS rely on a cost-effectiveness threshold.²⁹ Most clinical trials used for health authority registrations are not designed for these types of comparisons.³⁰

Cost-Effectiveness Studies

Unlike comparative effectiveness studies that focus more on clinical outcomes,²⁷ cost-effectiveness studies balance a single unit of cost against a single unit of risk or benefit to the quality of life extended to the patient (Table). This metric is known as the incremental cost-effectiveness ratio (ICER), and is the monetary cost of gaining an extra quality-adjusted life-year from each treatment.³ Many countries have adopted cost-effectiveness analysis models to analyze the cost-benefit ratio of existing technologies versus the advancement towards innovative new products.³¹ The United Kingdom's NICE and Australia's Pharmaceutical Benefits Advisory Committee report using preset thresholds when determining the utility of technological advancements with respect to treatment decision making.³¹ Fixed ICER

thresholds, which reflect the maximum cost per unit of outcome that a healthcare payer will pay for medicine, have now become part of the standard for reimbursement in many countries, including Australia, Canada, the United Kingdom, the Netherlands, New Zealand, the United States, and Sweden (Figure 4). Therapies that exceed the ICER threshold are unlikely to be recommended for reimbursement.³

Reference Pricing

Reference pricing is the price set by the payer for a group of similar drugs based on a benchmark, or the reference, price. The reference price may be based on the lowest-cost drug in the group or can be an average price of all drugs in that group. Reference pricing is used in countries with national or provincial health systems, such as Australia, New Zealand, Belgium, Germany, Hungary, Spain, the Netherlands, South Africa, and the Canadian province of British Columbia. With this type of reimbursement system, the consumer pays the difference between the manufacturer's price and the reference price.²⁹

Generic reference pricing refers to a set of drugs that are chemically equivalent, while therapeutic reference pricing differs in that it includes drugs that are therapeutically equivalent.²⁹ The general principle of therapeutic pricing is to include a set of drugs that physicians would consider appropriate for substitution for most patients.²⁹ Not all drug classes may be suitable, especially classes where clinical evidence of interchangeability is limited.²⁹ It has yet to be determined how the latter may have a potential use with biosimilars and therapeutic comparisons to their reference biologic drugs.

Cost-Minimization Analyses

Cost-minimization analyses can be used to evaluate the potential pharmacoeconomic benefits of

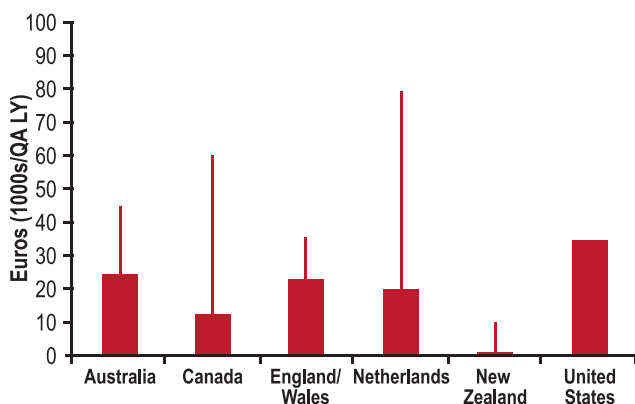


Figure 4. Range of threshold incremental cost-effectiveness ratios in selected countries (bars extend to upper limit; calculated per life-year). QALY = quality-adjusted life-year. Simoons.²⁰

biosimilars. These studies compare products with equivalent benefits to the patient, but with differing costs to determine the most economical treatment option.¹⁹ For example, a decision may be made to introduce a biosimilar rather than its reference biologic drug as it should provide the same benefit at a lower cost.⁹ These studies have been conducted in countries where biosimilars are already in use. Cost-minimization analyses from two phase III trials for biosimilars to epoetin alfa in patients with chronic renal failure in the United Kingdom demonstrated clinical equivalence for the biosimilar, epoetin zeta, compared with epoetin alfa, and concluded that epoetin zeta would yield equivalent efficacy in terms of surrogate end points of correction and maintenance of hemoglobin concentration that is economical according to a cost-minimization analysis.²⁰ In another study, cost-savings of £322 per patient over an 84-day period were predicted in a cost-minimization analysis for a biosimilar to filgrastim for the prevention of neutropenia in patients with breast cancer.²⁰ The results of cost-minimization analyses, although currently limited in number, may suggest a role of biosimilars in helping to address escalating cancer treatment costs while providing highly similar efficacy and safety to patients with cancer.

HOW MIGHT PHARMACOECONOMIC ANALYSES CONTRIBUTE TO TREATMENT DECISIONS?

Pharmacoeconomic analyses may help to inform healthcare professionals regarding therapeutic options that represent potentially beneficial and economical alternatives for patients and healthcare systems. With biosimilars, pharmacoeconomic analyses findings are impacted by development and manufacturing costs, monitoring and acquisition costs, as well as the determination of potential benefits to patients in terms of offsetting healthcare expenses.²⁰ For patients, a broader role for effectiveness research in formulary and drug benefit design may be advantageous, because decisions may be driven by overall value as opposed to solely by economics.²⁹ As biosimilars emerge and potentially become more widespread in clinical practice, additional pharmacoeconomic analyses may be performed and yield additional data on the effects of biosimilars on reducing cancer treatment costs, shedding greater light on the potential pharmacoeconomic benefits of these agents. Ultimately, the question may not be “Will biosimilars provide cost-savings?” Instead, it may be “Will they be cost-effective compared with their branded equivalents?”

As was the case in the EU, the adoption of biosimilars in the United States will not be driven

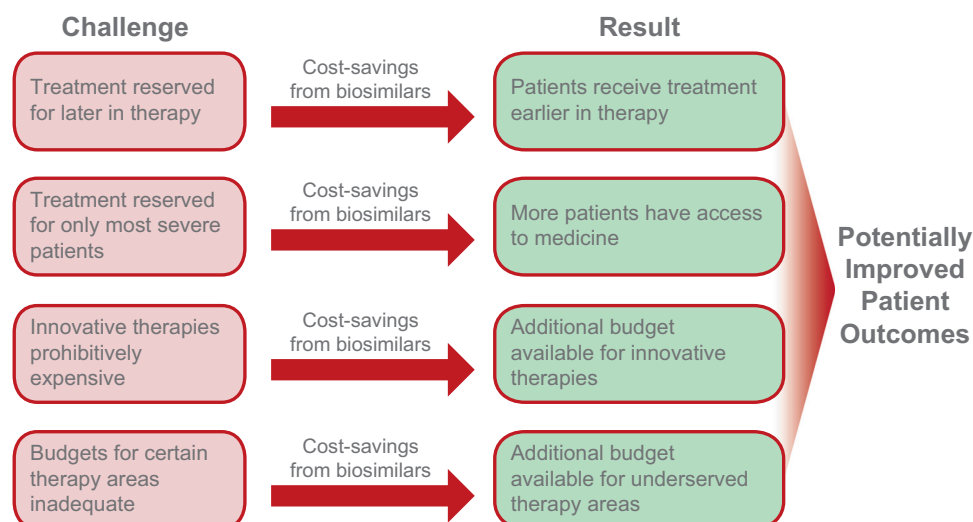


Figure 5. Savings with biosimilars could allow reallocation of budget to facilitate optimal patient treatment. Zelenetz et al.⁹; Weise et al.¹⁷; Gascon et al.¹⁸; Walley et al.¹⁹

solely by monetary concerns, but by safety and efficacy data.^{9,17} Savings from biosimilars also have the potential to enable use of biologic drugs (in the form of biosimilars) to patients who may not have had access to biologic therapies previously, leading to potentially improved patient outcomes which, in turn, may have a positive effect on cost-effectiveness models (Figure 5). Finally, the balance between the need for increased access *and* innovative therapies is a consideration that may be achieved through the additional competition and potential cost-savings associated with biosimilars.³²

CONCLUSIONS

The cost of cancer treatment is a leading driver of global healthcare costs, in part due to the use of expensive biologics. Biosimilars represent a potential opportunity to increase patient accessibility to biological therapies and lower the cost of treatment (Figure 5). The overall pharmacoeconomic evaluation of biosimilars may be affected by several factors, including their manufacturing and development costs, potential effect on comparative safety and efficacy of biosimilars to first-generation products by second-generation biologic drugs, safety monitoring costs, and institutional and/or government pricing policies. While there are limited pharmacoeconomic analyses reported for biosimilars in general, the cost-minimization studies reported for biosimilars used as supportive therapy in the oncology setting to date suggest biosimilars may have the potential to lower cost while offering efficacy and safety that is highly similar to their reference biologic drugs. Patients may regard the value of a biosimilar as that of an option that reduces the opportunity costs for healthcare or other expenses. As the

development and adoption of biosimilars continue to increase in the EU and potentially the United States and other countries, pharmacoeconomic analyses may be useful in evaluating biosimilars of two differing reference biologic drug products. As is the case in the EU, the adoption of biosimilars in the United States will not be driven solely by monetary concerns, but by safety and efficacy data. As the use of biosimilars increases, additional pharmacoeconomic studies will provide evidence that helps the community determine the cost-effectiveness of biosimilars relative to other therapeutic options. Ultimately, this information will be one part of a package of evidence that helps inform overarching treatment strategies.

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